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ORIGINAL ARTICLE

Observational study on patients' compliance with Irbesartan in essential hypertension "I Comply"



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KEYWORDS

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Abstract *Objectives:* Observational study to assess essential hypertension patient's compliance on Irbesartan, rationale for prescribing Irbesartan, profile of patient for whom it is prescribed, and assess patient/physician satisfaction.

Methods: Naïve/uncontrolled patients with essential hypertension; for whom physicians decide to prescribe Irbesartan-based-regimen are followed up for 4 months to assess compliance, tolerability, satisfaction, and identify reasons for prescription. Physicians were required to fill a case-report-form and a simple questionnaire to identify patients' characteristics, give reason(s) for prescription, and persistence/non-persistence of patients/physicians. Satisfaction, safety profile, and blood pressure control were also assessed.

Results: Total of 62.1% ($n = 3971$) of all screened patients ($n = 6399$, Naïve = 31.04%, uncontrolled = 68.96%) were prescribed an Irbesartan based regimen. Efficacy, safety, and cost; in that ranking order, were the main reasons for prescribing specific antihypertensive agent. By the end of the study, satisfaction for Irbesartan 150 mg, 300 mg, and 300 mg/12.5 mg was 95.6%, 96.8%, and 96.5%, respectively; up from 72.6% general patient satisfaction with their current regimen at screening visit. Physicians showed a similar improvement in satisfaction to 96.4%, 97.1%, and 95.8, respectively, up from 27.3% satisfaction with previous regimen. Patient's compliance increased up from 86% at the beginning of the study to a mean of 96.2% by the end of the study.

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Conclusion: A total of $96\% \pm 0.8$ of Irbesartan population were satisfied with their Irbesartan regimen. Reasons for prescribing a specific antihypertensive class were identified as efficacy, safety, and cost. Angiotensin-Receptor-Blockers were the antihypertensive of choice for 68.9% of physicians due to its efficacy (96.5%) and safety (85.9%). The majority (91.49%) of side effects were recorded as being 'mild', no serious adverse events were recorded.

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1. Introduction

Hypertension is one of the major cardiovascular diseases worldwide; in 2000; 26% of the adult population had hypertension.¹ It has been estimated that hypertension is responsible for 4% of the global burden of disease.² It is one of the major causes of morbidity and mortality in both developing and developed regions, particularly cardiovascular and renal diseases.³ Hypertensive heart disease, is the largest single contributor among the remaining causes of cardiovascular disease (CVD) morbidity & mortality,⁴ accounting for as much as 11% in the Middle East. And, out of the 17 countries of the middle East & North Africa (MENA) region, which represents 6% (306 million people), of the whole world's population, Egypt alone is the most populous country of the region, having 24% of the total inhabitants of the region.⁵

According to the National Health and Nutrition Examination Surveys (NHANES) III study in the United States, less than a quarter of hypertensive patients have their blood pressure (BP) in good control (under 140/90 mmHg).⁶ Hypertension is also a major health problem affecting more than 20% of the Canadian population.⁷ It has been estimated that in Canada, only 16% of hypertensive patients are controlled, 23% are treated but not controlled, 19% are not treated and 42% are unaware of their condition.⁸ In Egypt, a National Hypertension Project implemented in the 90s showed that Hypertension is affecting more than 26% of population above 25 years, only 8% of hypertensive patients are controlled, 16% are treated but not controlled, 14% are not treated with medications and 63% are unaware of their condition.⁹

One of the major factors in this poor control is the lack of patient adherence to treatment.¹⁰ Overall hypertensive patients are estimated to take only 53–70% of the medication prescribed for them.^{11–13} Furthermore, noncompliance, has been reported to be one of the main causes for refractory hypertension.¹⁴

In 1999 the total cost of treating hypertension in the United States (US) was estimated to be \$33.3 billion, including \$8.8 billion for lost productivity resulting from hypertension-related morbidity and mortality.⁹

Numerous studies have examined treatment persistence in hypertension. Some of these predated the introduction of newer drug classes.^{15–20} Most guidelines suggest that initial combination treatment should include a thiazide diuretic and either an angiotensin receptor blocker (ARB), an angiotensin-converting enzyme inhibitor (ACE-I), a calcium channel blocker (CCB), or a beta-blocker.^{6,21} Actually Sever PS and Messerli FH,²² in their latest article review, published in Oct 2011, in the European Heart Journal, under the title of Hypertension management 2011: optimal combination therapy, they enlist, ARB + diuretics combination as the PREFERRED one, as the activation of RAAS system due to intravascular volume depletion by diuretics, is mitigated by the addition of RAAS blocker.²¹ In addition,

for patients with chronic renal disease or type 2 diabetes, combinations including an ARB or ACE-I are recommended²³ however, with caution due to the possible combined hyperkalemic effect of both agents, in this particular subset of patients. The usefulness of fixed dose (FD) ARB/hydrochlorothiazide (HCTZ) combinations in effectively treating hypertension, including difficult-to-treat and severely hypertensive patients, has been demonstrated for several different ARBs.^{16,24} Promising results have also been reported for FD combinations regarding improvements in clinical endpoints, as well as achieving BP targets. In addition, combining HCTZ with an ARB attenuates the hypokalemic and fasting glucose-modifying effects of HCTZ. Also, there is evidence to suggest that FD combinations are also associated with better compliance.²¹

Irbesartan has no active metabolite, and a terminal half-life of 11–15 h, accounting for its single daily use, potent, angiotensin receptor 1 (AT1) receptor antagonist, with high selectivity for the AT1 receptor subtype. Results of recent clinical studies show that irbesartan safely and effectively lowers BP within 1 week in patients with mild-to moderate hypertension.^{6,24,25}

This study was designed with the main objective of evaluating both; compliance in patients, and persistence of both patients and physicians to Irbesartan therapy. We looked at the general acceptance of the Irbesartan therapy among patients and physicians, and examined the relationship between satisfaction and compliance as a major factor in determining persistence, and eventually control of BP.

2. Subjects and methods

2.1. Study design

This national, multicenter, prospective product registry conducted in Egypt, in around 220 sites, comprised an initial screening visit where 6399 patients with essential hypertension, either newly discovered or uncontrolled on current regimen were screened for compliance, satisfaction with their current antihypertensive regimen, and main reasons for dissatisfaction. Furthermore, the reason for prescribing a specific antihypertensive drug by physicians was documented. Only patients for whom physicians decided, to prescribe an Irbesartan-based regimen (IBR) (3971 patients, 62.05%), were followed up for four months for their compliance and tolerability to prescribed regimen. At the End of study (EOS), all participating physicians were asked to fill a two page case report form (CRF) to point out the basic characteristics of the individual patient profile, the reason behind the choice of the antihypertensive regimen, and a questionnaire to assess the extent and reasons for persistence or non persistence on therapy. BP was documented at screening visit and at the EOS. Patient and physician satisfaction with the Irbesartan therapy was also documented.

2.2. Patients

Male or female patients aged > 18 years, with essential hypertension, whether newly discovered or uncontrolled on current regimen were screened (6399 patients, 100%). Patients eligible for follow-up (3971 patients, 62.05%) were those whose treating physicians decided on their own medical judgment to prescribe an IBR. The main exclusion criteria were; severe hypertension (systolic blood pressure (SBP) > 180 mmHg, and/or diastolic blood pressure (DBP) > 110 mmHg), secondary or malignant hypertension, pregnant or nursing women, and those of child-bearing potential, patients on dialysis or recent cardiovascular (CV) accident within the last 3 months.

2.3. Observations

Data were collected at screening visit and after 4 months during the follow-up visit, in the form of a CRF filled by the participating investigators to answer the key study questions. Collected data included patient's age, sex, profile (naïve, uncontrolled on current regimen), duration of hypertension, satisfaction and compliance with previous regimen. During the follow up phase, patients were monitored for their BP using BP monitors at investigators' sites, heart rate, missed doses, adverse events (AEs) and actions required; if any. Any change in therapy (i.e. dose changes, add-on therapy, switch to other antihypertensive agents, discontinuation) was also recorded, together with the reason for the change. At the EOS, the opinions of both, patients and physicians and their level of satisfaction with the current regimen were recorded.

3. Statistical analysis and sample size calculation

The targeted population size to be followed up on Irbesartan based regimen was estimated to be around 2300 patients, based on the fact that Irbesartan was prescribed to about 4% of hypertensive patients in Egypt, and assuming a compliance of 60–70% on Irbesartan as proven in the ICE project.²⁶

Descriptive methods were used for the analysis of the primary and secondary outcomes, including calculation of appropriate measures of the empirical distribution (mean, standard deviation, median, minimum, maximum, for continuous variables, and frequencies and percentages for categorical variables) as well as calculation of descriptive *p*-Values for group comparisons. Quantitative data were analyzed for normal distribution using paired *t*-test and repeated measures analysis. Qualitative data were analyzed using Chi square test.

4. Satisfaction and compliance assessment

Recruited patients were followed up for 4 months regarding their compliance to prescribed regimen, and the reason for non-compliance was documented together with the average number of missed doses. The level of satisfaction with current regimen was also documented at the EOS based on both; patient's and physician's opinions.

4.1. Efficacy assessment

The study, although had no endpoints regarding the efficacy of the treatment, we elected to analyze the BP values measured at

screening visit and again at the time of BP control (or EOS), for mean reduction in BP compared to baseline values, and provide an estimate of the overall efficacy. Changes to antihypertensive regimen were also recorded, indicating the reason for the change and the add-on or target regimen instituted.

4.2. Safety assessment

Patients were followed up for occurrence of any AE, serious adverse event (SAE), intensity of such events, and their relation to Irbesartan treatment. Sequelae, remedies, and outcome, including discontinuation of therapy, were also recorded.

5. Results

5.1. Recruitment

As represented in Fig. 1, out of 6399 screened patients, Irbesartan regimen was prescribed for a total of 3971 (62.05%) patients, of whom, 2275 patients (57.29%) representing the Irbesartan follow-up population were followed up and attended the EOS visit, while 1696 patients (42.70%) were lost to follow up – IBR drop-out population.

5.1.1. Patient baseline characteristics

As shown in Table 1, the mean age of patients was 52.8 ± 9.59 years. Males represented 57.2%, while females represented 42.8%. The mean SBP was 158.6 ± 13.58 mmHg while the mean DBP was 97.67 ± 6.62 mmHg. Treatment naïve (newly discovered hypertension) patients constituted 31.04% of the screened patients, while 68.96% were already on anti-hypertensive medication at screening with mean treatment duration of 33.28 ± 22.01 months. Patients' hypertension history is listed in Table 2.

5.2. Drivers for choice of antihypertensive regimen

ARBs were the most frequently prescribed anti-hypertensive medications. They were prescribed for 68.9% of the total screened population, followed by ACE-Is, beta-blockers, diuretics, and calcium-channel blockers at a prescription rate of 10.5%, 9.3%, 7.2%, and 4%, respectively.

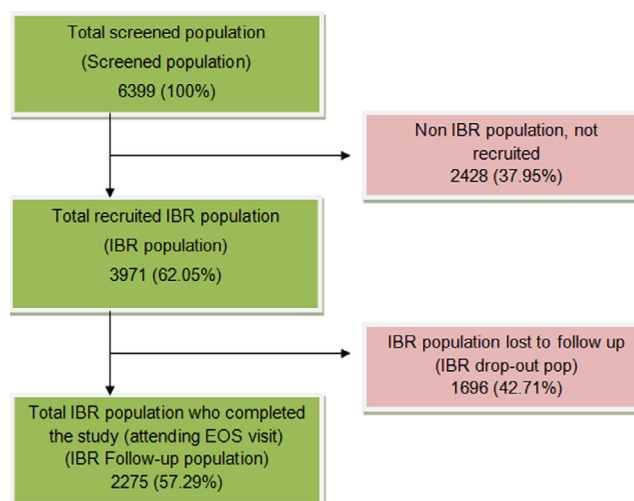


Figure 1 Recruitment outline.

Table 1 Patients' baseline characteristics and demographics.

	Patients on IBR 3971 (100%)	Enrolled population 6399 (100%)
Mean age (\pm SD) – years	52.84 (9.437)	52.8 (9.587)
<i>Sex</i>		
Male	2310 (58.2)	3662 (57.2%)
Female	1661 (41.8)	2737 (42.8%)
Mean SBP (\pm SD) – mmHg	160.443 (12.664)	158.6 (13.583)
Mean DBP (\pm SD) – mmHg	98.57 (6.484)	97.67 (6.622)
Heart rate (\pm SD) – beat/min	82 (9.458)	81 (9.847)
<i>Medical history</i>		
Previous significant diseases	774 (19.5)	1212 (18.9)
Ongoing diseases	2339 (58.9)	3655 (57.1)
Diabetes mellitus	1586 (39.9)	2476 (38.7)
Dyslipidemia	1158 (29.2)	1747 (27.3)

Table 2 Hypertension history.

	Patients on IBR 3971 (100%)	Enrolled population 6399 (100%)
<i>Hypertension duration (months)</i>		
Mean	38.48	40.54
\pm SD	27.87	29.59
<i>Patient status</i>		
Naive	1249 (31.5)	1986 (31.04%)
On anti-hypertensive medication	2722 (68.5)	4413 (68.96%)
<i>Duration of last antihypertensive (months)</i>		
Mean	29.7	33.28
\pm SD	18.82	22.01

Among all treatment groups, three factors were identified as the main drivers for antihypertensive drug choice, namely: efficacy (mean = 85.92% of patients), safety (mean = 62.3% of patients), and cost (mean = 39.64% of patients).

In patients who were on Irbesartan (IBR follow-up pop., $n = 2275$), 240 (10.5%) required a change in therapy at the end of the study, the reasons for the choice of the newly prescribed medication were efficacy for 88.33%, safety profile for 60.83% and cost for 15.83% of patients requiring a therapy modification.

5.3. Satisfaction and compliance

5.3.1. Patient and physician satisfaction with antihypertensive medications – “all non-naïve screened patients” – $n = 4413$

As represented in Fig. 2, in the total screened population; patient and physician input concerning the satisfaction and dissatisfaction related to previously prescribed anti-hypertensive medication, at screening visit, were as follows; out of 4413 patients on anti-hypertensive therapy, 38.3% of patients were satisfied with their medication. On the contrary, 61.7% were not satisfied. Reasons for dissatisfaction included insufficient BP control (52.3%) or side effects (24%). According to physicians' opinion; they were satisfied with the antihypertensive medication for 32.3% of patients, while dissatisfied for 67.7% of patients. Reasons for physicians' dissatisfaction included insufficient BP control (59.2%) and side effects (22.1%).

85.6% of patients were compliant to their antihypertensive medication at screening visit while 14.4% were non compliant with an average of 2.75 ± 1.24 missed doses per month.

5.3.2. Patient and physician satisfaction in patients already on an IBR at screening visit ($n = 2722$)

Out of 2722 patients who were already on a previous IBR at screening visit, 27.4% of patients were satisfied with their previous Irbesartan-based medication. On the contrary 72.6% were dissatisfied. Reasons for dissatisfaction included

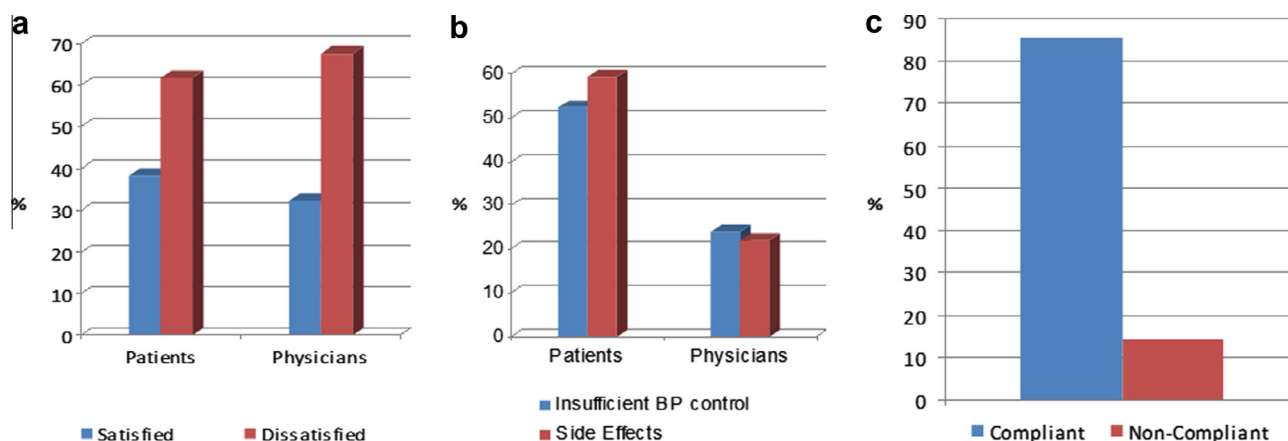


Figure 2 Satisfaction and compliance of naïve patients. (a) Satisfaction/dissatisfaction, (b) reason for dissatisfaction, and (c) compliance.

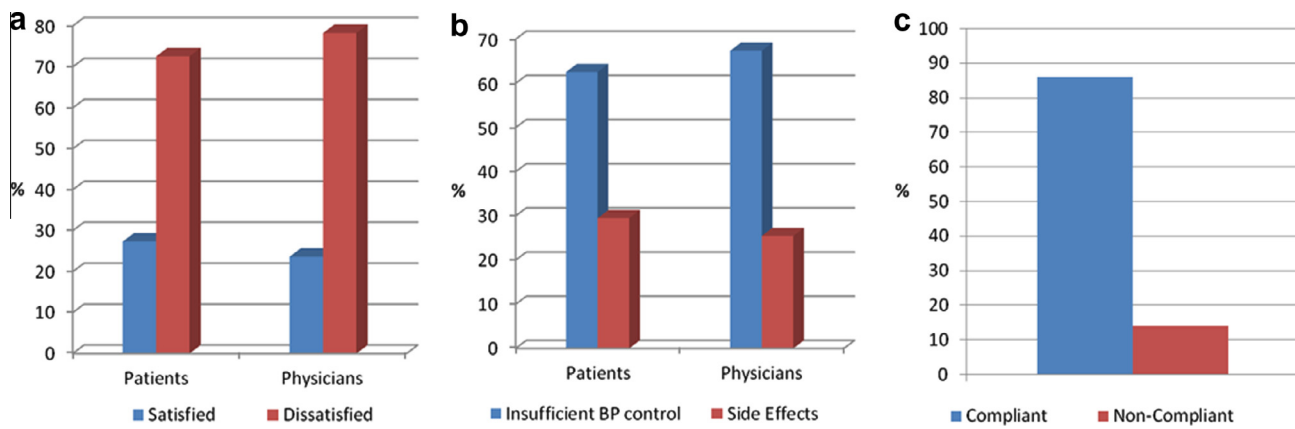


Figure 3 Satisfaction and compliance of patients already on Irbesartan at screening visit. (a) Satisfaction/dissatisfaction, (b) reason for dissatisfaction and (c) compliance.

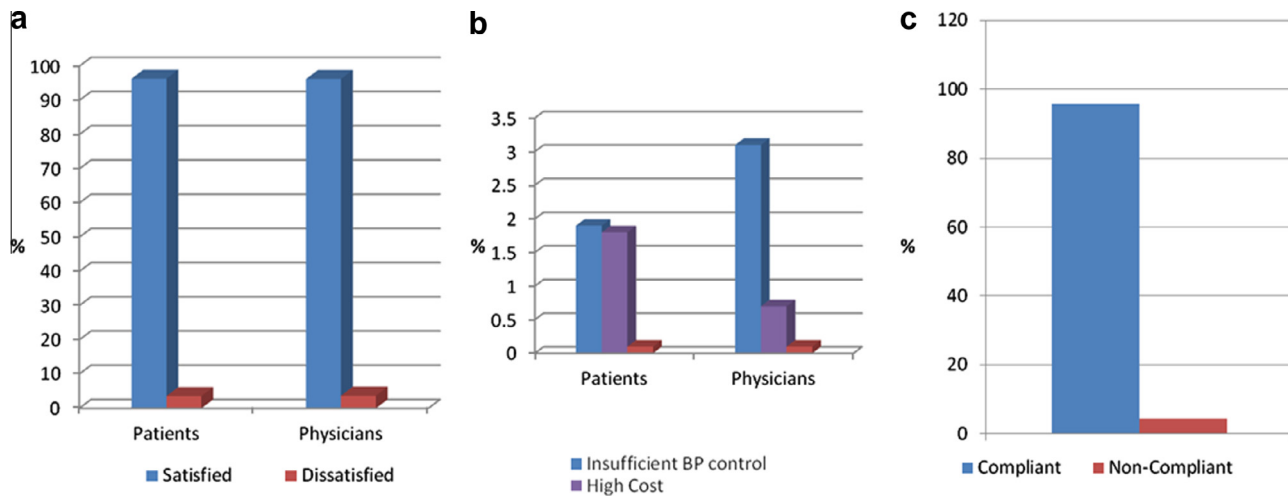


Figure 4 Satisfaction and compliance of patients at the end of study. (a) Satisfaction/dissatisfaction, (b) reason for dissatisfaction and (c) compliance.

insufficient BP control (62.6%) and side effects (29.5%). According to physicians' opinion; they were satisfied with the previous Irbesartan-based medication for (23.7%) of patients, while dissatisfied for 76.3% of patients. Reasons for physicians' dissatisfaction included insufficient BP control (67.4%) and encountered side effects (25.5%). Patients (86%) were compliant to their current antihypertensive medication at screening visit, while 14% were non compliant with an average of 2.37 ± 1.03 missed doses per month. The data are demonstrated in Fig. 3.

5.3.3. Patients' satisfaction with IBR at follow up visit ($n = 2275$)

At the follow up visit as shown in Fig. 4, patients showed a significant increase in their satisfaction rate where 96.4% of patients were satisfied with their Irbesartan treatment (P value < 0.001). On the contrary, 3.6% of patients were not satisfied with their Irbesartan treatment. Reasons for dissatisfaction included, insufficient BP control, high cost or side ef-

fects in 1.9%, 1.8% and 0.1% of patients, respectively. Physicians showed a significant increase in their satisfaction rate to reach 96.3% satisfaction with Irbesartan therapy compared to previous antihypertensive medications (P value < 0.001), while dissatisfaction was reported for 3.7% of physicians. Reasons for physicians' dissatisfaction included insufficient BP control, side effects and cost of medication for 3.1%, 0.1% and 0.7% of patients, respectively. Subsequently, improvement in both patients' and physicians' satisfaction was reflected on the compliance of patients to Irbesartan based regimen, which was significantly improved. Patients (95.7%) showed compliance to Irbesartan (P value < 0.001).

5.4. Heart rate and BP changes

At follow up, overall patients on Irbesartan based regimen showed a significant mean reduction of 30.39 ± 1.47 mmHg in SBP and 16.33 ± 1.45 mmHg in DBP (P value < 0.001).

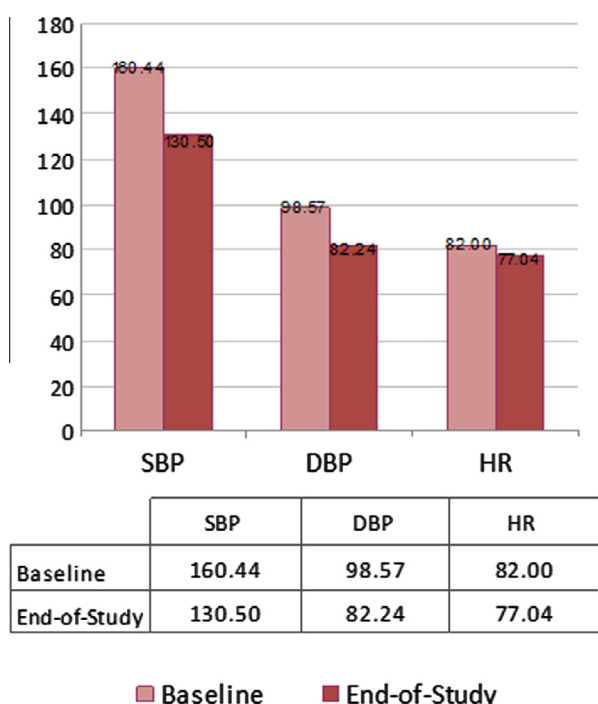


Figure 5 Baseline vs. End-of-study values.

Also, heart rate showed insignificant mean reduction as represented in Fig. 5.

5.5. Change of therapy

As shown in Fig. 6, out of the 2275 patients who attended the follow up visit, 240 patients (10.5%) had their therapy changed including dose changes; 155 patients (6.8%) had an add on

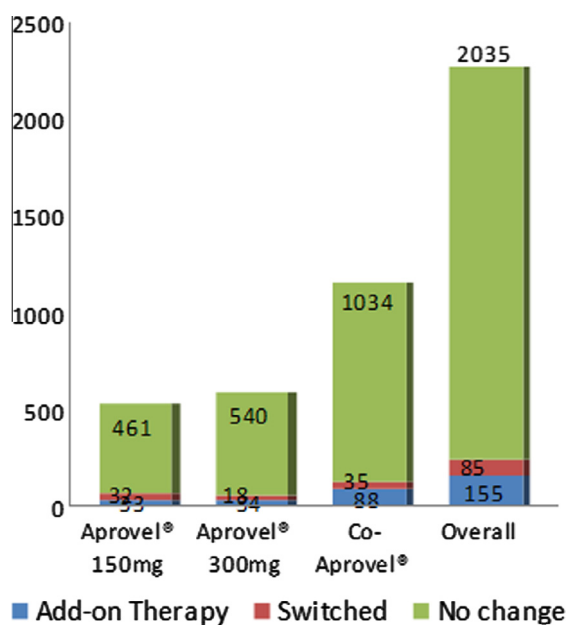


Figure 6 Change of therapy.

therapy and 85 patients (3.7%) had their therapy replaced. Reasons for change of therapy included; ineffectiveness, poor tolerance, and high cost in 140 (6.2%), 61 (2.7%) and 32 (1.4%) patients, respectively.

5.6. Safety profile

The safety was analyzed using the data from all patients on IBR population, $n = 3971$. Out of 3971 patients, AEs were reported in 137 (3.45%) patients. These AEs were mild to moderate in intensity with probable causal relation to study medication in 105 (2.85%) patients. All AEs experienced were not-serious and recovered without any sequelae.

Dizziness was the most common reported AE, being reported by 55 (1.39%) patients. Gastro-Intestinal Tract (GIT) disturbances were the second most common AEs reported by 47 (1.18%) patients. Headache, musculoskeletal pain and allergy were reported by 27 (0.68%), 6 (0.15%) and 2 (0.05%) patients respectively.

6. Discussion

This study showed that there is a strong relationship between efficacy, safety and compliance. Patients not controlled on their antihypertensive regimens are likely to lose confidence in the effectiveness of their medication, and gradually develop non compliance, which in turn affects the patient's overall persistence and willingness to continue receiving their medications. On the other hand, an effective medication possessing numerous undesirable side effects, have a similar impact on compliance. Accordingly, efficacy and safety cannot be separated when dealing with patient non compliance.

During the follow up visit, although we expected a great improvement in patient satisfaction and compliance, the improvement was beyond our expectations. 96.4% of patients were satisfied with Irbesartan regimen compared to 27.4% at the beginning of the study (screening visit), and 95.7% of patients showed improved compliance compared to 86% at screening visit.

This study demonstrated that the use of an antihypertensive regimen that is both effective and safe, can positively and significantly influence patient's satisfaction and compliance. It is clear that the patients only represent one side of the equation; physicians also need to have a similar confidence in the medication, to be willing to prescribe it, and hence, allow the patient to inherit a similar confidence.

This study showed that the provision of Irbesartan as an effective and safe antihypertensive agent, promoted patient compliance, and eventually lead to patients' persistence on therapy, which is likely to be reflected on their quality of life (QOL) as well.

In addition, the economical impact of efficient BP control (achieved through the use of an effective regimen in a compliant patient), especially in developing countries, should not be overlooked.

Although this study has investigated the relationship between efficacy, safety, and patient's compliance, other factors known to affect compliance still need to be examined, including daily frequency of administration, ease of use and patient awareness. Future studies should consider incorporating a

wider range of factors to examine the interactions between these factors and their collective impact on the overall compliance.

7. Conclusion

Out of the total screened patients, Angiotensin II Receptor Blockers (including all forms of Irbesartan) were the most prescribed anti-hypertensive medications, being prescribed to 68.9% of the total screened patients. Patients (31.5%) prescribed an Irbesartan-based regimen were naïve, while 68.5% were already on an antihypertensive regimen. The main drivers for prescribing antihypertensive drugs were identified as efficacy, safety profile and cost of the prescribed medication.

Irbesartan based regimen as an antihypertensive agent for the treatment of essential hypertension showed a significant improvement in the satisfaction rate of both, patients and physicians, compared to previous medications that was reflected on the compliance of patients, which was significantly improved. 95.7% of patients showed compliance on Irbesartan compared to their previous antihypertensive medications. Persistence rate for Irbesartan based regimen during the study duration was 89.5%. Physicians (96.3%) were satisfied with the Irbesartan regimen, at the follow up visit (compared to 23.7% at screening visit).

Patients on Irbesartan based regimen showed a significant mean reduction of 30.39 ± 1.47 mmHg in SBP and 16.33 ± 1.45 mmHg in DBP.

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